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A Vision Becoming Reality

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Summary — Non-animal science in toxicology and health research has been progressing for decades, but only now is it being seen widely as advanced science. The emergence of novel human biology-based tools and models, combined with legislative and regulatory change, a 21st century concept for toxicology, continuing failures in the drug pipeline, and systematic critiques of animal models, have created a pivotal moment of change. The leading edge is starting to become the norm. Humans and other animals are likely to benefit as a result.

Key words: 21st century toxicology, health research, non-animal methods, replacement.

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Introduction

Possibly the only advantage to broaching your sixth decade is the dubious pleasure of taking the long view of what has gone before (and why). Probably the major drawback is that you risk becoming one of those boring seniors who only talk about the past. But, since those who ignore history are condemned to repeat it, this piece aims to look at the replacement of animal experiments in a timeline running from the past to the future, and from a distinctively personal viewpoint.

Starting with the present, stretched slightly to include 2007, I suggest the turning point for non-animal science has to have been the publication of the US National Research Council's (NRC) ground-breaking report on 21st century toxicology (1).

A new Nobel Prize?

I'm embarrassed to say that, despite the wisdom of years, I didn't fully realise the significance of the NRC report when it was first published; but subsequent developments have been so positive that I would want to nominate the authors of the report for the Nobel Prize for Replacing Animal Experiments. And that would be ironic, because the whole drive, reason and focus of that extraordinary report was to do better, 21st century, science — and not primarily to replace animal tests. The authors understood that advanced science had to mean less reliance on animal tests, and they found a way to convince scientific leaders around the world of this truth.

The authors' "vision" was to see that the only way toxicology could respond to modern demands was to throw out the conventional approach entirely, and their "strategy" was to develop a crazy new paradigm for safety testing. Their proposal — to move away from the measurement of apical endpoints in animals (the black-box approach for more than 60 years) toward an understanding of human pathways of toxicity that disrupt healthy function in cells, organs and individuals — was an ambitious masterstroke.

Quantitative structure–activity relationships (QSARs) would be followed by high-throughput *in vitro* biological screening assays to detect toxic perturbations in gene, protein and other cellular pathways, by using molecular and cellular tools. More in-depth information would derive mainly from high-content cellular assays, or three-dimensional tissue constructs, using human cells wherever possible. Animal studies would be resorted to only occasionally and from necessity. The data generated would be integrated and extrapolated for hazard identification and risk assessment, by using systems biology and related tools.

This conceptual transformation in toxicology only became possible because of pragmatic developments in science over the last decade or two, such as the Human Genome Project, the whole suite of 'omics' techniques (2), the potential of adult human induced pluripotent stem cells (3), tissue engineering (4) and microfluidics (5), multiplexed high-content analytical tools (6), and massive advances in bioinformatics (7).

It was the genius of the NRC authors to recognise and seize this scientific turning point, and to present their plan as a realistic concept that is

^aThe author was a member of the 2012 Lush Prize judging panel.

achieving huge buy-in from essential stakeholders. The first impact of their vision and strategy was subsequently intensified by workshops, special issues of journals, high-quality media coverage, and new government, industry and NGO consortia and initiatives, set up to progress the work globally. You will recognise the diverse cast of characters, including the US multi-agency Tox21 consortium (8), the Environmental Protection Agency's ToxCast programme (9), the European Union's AXLR8 coordination action (10), the Transatlantic Think Tank of Toxicology (11), the Human Toxicology Project Consortium (12), and the Adverse Outcome Pathway programme (13) of the Organisation for Economic Co-operation and Development (OECD), among others.

One aspect of my recent work as Senior Scientific Advisor to Humane Society International (HSI) has been to help promote the 21st century toxicology transition in the European Union (EU). In 2012, HSI organised a European Parliament workshop hosted by Mario Pirillo MEP, on advancing safety science and health research under Horizon 2020 with innovative, non-animal tools. My report of the same title was launched at the workshop (14), and speakers from different member states presented their research in support of that theme. Representing HSI, I suggested that the medical research community needs to consider its own paradigm change, moving the strategic focus of disease modelling and drug discovery away from animal experiments and toward understanding human disease pathways by using advanced research techniques. That the 2013 EU draft agreement on a specific programme implementing Horizon 2020 has recognised the value of essential technologies, such as bioinformatics and systems biology, the 'omics', molecular tools and cell-based platforms, is a good first step.

Today Toxicology, Tomorrow Health Research

Most of my career as an 'animal rights scientist' has straddled the medical research/toxicology divide. I became head of science at the Dr Hadwen Trust for Humane Research in 1979, when cell culture was only two-dimensional and relied solely on rather abnormal immortalised cell lines, and computer modelling was little more than a gleam in Dorothy Hegarty's eye (the founder of FRAME recognised the potential of computational modelling long before most of us). We developed the prototype of the Bovine Corneal Opacity and Permeability (BCOP) assay for eye irritation during the 1980s (15–17). In 2009, after quarter of a century, it was accepted by the OECD as a partial replacement for the Draize rabbit eye test for identifying corrosives and severe eye irritants, and in 2013, it was one of the first *in*

vitro tests to be approved for characterising chemicals as non-irritant (18).

The Dr Hadwen Trust was the first funder to recognise the potential for replacing animals of new functional neuroimaging and related techniques, with its support for magnetoencephalography in 1992 (19), and in 1998 for transcranial magnetic stimulation as a 'virtual' lesioning technique (20). Those technologies have partly replaced electrophysiological and lesioning experiments on non-human primates (21) with non-invasive studies of the human brain (22, 23).

One of my early forays into non-animal toxicology was to research and write an in-depth report for Constantine and Weir (whose mail order business, Cosmetics to Go, was Lush's predecessor), called *Alternatives to Animal Tests in Cosmetic Toxicology*. It was produced in 1990 as a technical submission to the European Commission regarding the Cosmetics Directive (76/768/EEC). For the time, it was a pioneering and comprehensive review of potential *replacement* methods, including computer modelling, Neutral Red and MTT cytotoxicity assays, QSARs, human skin samples *in vitro*, volunteer studies, and much more. The RSPCA Research Animals Department hailed it as "a great work... enormously useful to the Department". My long relationship with the ever-changing Cosmetics Directive goes back to its 1980 incarnation. I was introduced to it by the then managing director of Yardley, who recognised that it would increase animal testing, which it did. Latterly, of course, it has reversed that direction, definitively.

In terms of implementing animal *replacement* techniques and policy development, although the pace has sometimes seemed glacial, toxicology has always been ahead of medical research. My plenary lecture at the Third World Congress on Alternatives in 1999 emphasised that while non-animal safety tests were progressing, disease research and drug discovery faced different challenges: research questions were more open-ended and the research enterprise not so constrained by regulatory and legislative changes. For example, whilst the Cosmetics Directive was constantly amended as public concern about animal testing increased, medical researchers were insulated from this type of influence and were more focused by pressures such as conservative peer-review and established funding policies (24). It's a theme I've pursued for a long time in an effort to shift the framework of health research away from its animal model focus (25).

A 'Macro-change' Moment

We always considered non-animal techniques to be ethically advanced, but it's only in this century that the required scientific tools have emerged to

really justify the claim, across the board, that human biology-based approaches are genuine advances. 'Humane science' has become 'advanced science'. In health research, systematic analyses of the performance of animal models will likely be important in driving progress (26). As long as researchers are allowed to remain in denial about the validity of their animal models, they will not consider significant change. I suggest that systematic reviews and meta-analyses of the predictivity of animal studies will continue to show that species barriers can never be entirely designed away, and that the emperor has no clothes (or at least, little more than flimsy underwear).

You probably *have* to be an optimist to sustain a three-decade career in animal rights science with your sanity intact. There is no doubt there are many sizeable technical, conceptual and policy barriers to overcome. It has never been enough to simply fund non-animal *replacement* research and testing methods: constant advocacy and promotion are essential. I've always enjoyed gauging the precise optimum between a confrontational approach, which repels many people, and a passive politeness, which persuades no-one of the need for change. As a member of the government's Animal Procedures Committee (1998–2006), I honed that talent to a knife-edge, and saw quite dramatic progress in the nature of the committee's working processes over those years.

Looking in the rear-view mirror, so to speak, the times when progress seemed out of reach were probably times of multiple micro-changes, each too small to notice. But at a certain threshold, macro-change erupts and the leading edge starts to become the norm. It's difficult to predict those moments, but we are living through one now: a coming-together of advanced scientific and technological developments gaining widespread recognition; legislative and regulatory change providing the setting; a new concept for toxicology being articulated; continuing disappointments in the drug pipeline worrying the pharma industry (27); and ongoing critiques of animal models appearing in the literature (28–32).

Together these have created a synergy with irresistible momentum. For a long time, many of us have shared a vision of doing excellent science without harming animals, and at this pivotal moment it seems it can become a reality. If so, all of us — humans and other animals together — will benefit.

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